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RESEARCH ARTICLE

Impact of Melatonin, Zaleplon, Zopiclone, and Temazepam on Psychomotor Performance

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Introduction: Modern military operations may require pharmaceutical methods to sustain alertness and facilitate sleep in order to maintain operational readiness. In operations with very limited sleep windows, hypnotics with very short half-lives (e.g., zaleplon, t½ 1 h) are of interest, while with longer sleep opportunities, longer acting agents (e.g., zopiclone, temazepam (t½ 4–6 hours) may be used. This study was designed to compare the effect of a single dose of zaleplon, zopiclone, temazepam, and melatonin on psychomotor performance and to quantify the post-ingestion time required for return to normal performance. ***Method:*** There were 25 subjects (9 men, 14 women), 21–53 yr of age, assessed for psychomotor performance on 2 test batteries (4 tasks) that included a sleepiness questionnaire. Psychomotor testing was conducted prior to, and for 7 h after, ingestion of a single dose of each of placebo, zaleplon 10 mg, zopiclone 7.5 mg, temazepam 15 mg, and time-released melatonin 6 mg. The experimental design was a double-blind cross-over with counter balanced treatment order. ***Results:*** Zaleplon, zopiclone, and temazepam impaired performance on all four tasks: serial reaction time (SRT), logical reasoning (LRT), serial subtraction (SST), and multitask (MT). Melatonin did not impair performance on any task. The time to recovery of normal performance for SRT during the zaleplon, zopiclone and temazepam conditions were 3.25, 6.25, and 5.25 h respectively; for LRT were 3.25, >6.25, and 4.25 h; for SST were 2.25, >6.25, and 4.25 h, and for MT were 2.25, 4.25, and 3.25 h. The recovery time to baseline subjective sleepiness levels for zaleplon, zopiclone, temazepam, and melatonin were 4.25, >6.25, 5.25, and > 4.25 h, respectively. ***Conclusions:*** In spite of a prolonged period of perceived sleepiness, melatonin was superior to zaleplon in causing no impact on performance. The remaining drugs listed in increasing order of performance impact duration are zaleplon, temazepam, and zopiclone.

Keywords: chronobiology, hypnotics, performance, military operations

THE SCIENCE of chronobiology is yielding advances in fatigue management through the use of pharmaceuticals both to facilitate sleep (22) and to sustain alertness (25). While there is some interest in these approaches within the Army and Navy, to date, most of this research has been in support of Air Force aircrew. During the Falkland Islands War, the RAF used benzodiazepenes (primarily temazepam) to facilitate sleep in their aircrews (22). Benzodiazepenes are effective in the treatment of insomnia (11) and have a greater margin of safety than barbiturates (17), but they can have adverse effects on psychomotor performance as well as on memory and can cause next day hangover effects. Some benzodiazepenes have potential for abuse, but less than their barbiturate predecessors (28).

Newer generation sedative/hypnotics with shorter half-lives are of particular interest for promoting sleep hygiene and crew rest. Zaleplon (Starnoc®), a new sedative/hypnotic, has a half-life of about 1 h, and reaches peak plasma concentrations in 0.9–1.5 h. In contrast to zaleplon, zopiclone (Imovane®) and temazepam (Restoril®) have 4-h and 6-h half-lives, respectively. All three of these medications are prescription drugs approved by Health Canada.

The purpose of this protocol was to compare the effects of zaleplon, zopiclone, temazepam, and melatonin against a placebo, not on their ability to induce sleep, but for their impact on psychomotor performance after ingestion of a single dose, and to quantify respective post ingestion times to return to normal performance. The rationale for this paradigm is that in some military operations, personnel may be required to awaken from sleep to perform duties after having taken a hypnotic to induce sleep. This study was designed to assess the performance effects of hypnotics that may be used in such operational settings.

Based on our review of these pharmaceutical sleep-facilitating preparations, we expected temazepam to cause the most profound and the longest lasting impact on psychomotor performance, followed in order of decreasing impact by zopiclone, zaleplon, and melatonin.

METHODS

This was a completely repeated measures design where all subjects received all treatment conditions (a single dose each of placebo, zaleplon, zopiclone, temazepam, and Circadin®, a time-released pharmaceutical preparation of melatonin). There were 6 d for drug washout between treatments. The study was double

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blind with counterbalanced treatment order. The Defence Research and Development Canada (DRDC) Toronto Human Research Ethics Committee (HREC) approved this protocol.

The subjects were 23 volunteers (9 men and 14 women) from DRDC Toronto (military and civilian), between 21 and 53 yr of age. The mean subject age ± SD was 29.9 ± 10.3. All subjects provided written informed consent in accordance with the declaration of Helsinki. Before being accepted into the study, all volunteers first passed a screening medical that eliminated any subjects for whom these medications were contraindicated or subjects who were taking other medications. Because any of these medications (zaleplon, zopiclone, temazepam, or melatonin) could be potentially harmful to a fetus, any woman who wished to participate was first required to undergo medical screening to preclude pregnancy. In order to avoid contaminating psychomotor test results, subjects were instructed to abstain from the use of hypnotics or psychoactive drugs (tranquilizers) for 2 wk before any psychomotor testing, and from alcohol or over-the-counter medications within 12 h of psychomotor testing. The subjects were instructed to maintain regular sleep-wake cycles during the study and were asked to fill in a daily sleep questionnaire on awakening for three days prior to each experimental session to confirm normal sleep patterns. Subjects were compensated for their participation according to the DRDC Toronto guidelines for subject stress allowance.

Prior to commencement of the study, all subjects were trained to asymptote performance on two psychomotor test batteries: a) a subset of the DRDC-Toronto SUSOPS (sustained operations) battery to measure SRT (serial reaction time) (35), LRT (logical reasoning) (2), and SST (serial subtraction task) (15) and b) a multitask (MT) test battery (34) recently developed under the auspices of Transport Canada, and designed to simulate the information processing characteristics of flight performance. All psychomotor tasks were administered from laptop computers. The three SUSOPS tasks took 10 min to complete including completion of the Stanford Sleepiness Scale. Three minutes were devoted to complete the SRT to assess psychomotor speed, in turn followed by 5 min of LRT to measure higher order cognition, and finally by 3 min of SST (which has an embedded short-term memory component) to evaluate mental arithmetic capacity. The SUSOPS task battery was followed by the MT, which took 15 min to complete and which involves tracking toward various targets (waypoints) while attending to a flight director, monitoring attitude indicators for discrepancies, remaining vigilant for altitude command changes, and operating a tracking task analogous to the operation of the power quadrant of a large multi-engine transport aircraft. Completing both task batteries (all 4 tasks) took 25 min. Training on the psychomotor tasks required 12 iterations of each task or approximately 6 h of training.

Immediately prior to, and immediately after each psychomotor test session, the subjects underwent 4-min eyes-closed rest periods. We assessed the relative efficacy of these hypnotics to induce microsleeps by measuring EEG during these rest periods. These EEG results will be reported elsewhere.

For each treatment condition, subjects reported to the laboratory at 0800 hours. They performed a baseline psychomotor test session before being fitted with EEG electrodes and ingesting a single dose of medication at 0945 hours. Thereafter, the subjects were tested for psychomotor performance once every hour for 7 h, commencing at the 'top of the hour.' Each subject had at least 6 d between test doses to allow for drug washout.

The test doses were standard clinical doses (zaleplon 10 mg, zopiclone 7.5 mg, temazepam 15 mg in a hard-gelatin capsule), as well as Circadin® 6 mg (a pharmaceutical grade time-released melatonin formulated by Neurim Pharmaceuticals in Tel Aviv, Israel), which we used in earlier work (24). Prior to the study, regulatory approval for the use of Circadin® was obtained from the Therapeutic Products Directorate of Health Canada. In order to maintain the double-blind nature of this work, all medications were prepared in identical capsule format by a contract pharmacy (Central Medical Pharmacy, Toronto, Canada). All medications were administered blind by the principal investigator or his designate in accordance with the dosing protocol established by the contract pharmacy. Because all subjects were in our care and control from 0800 to 1700 hours, noon meals were provided.

In order to correlate changes in psychomotor performance over time, serial drug levels were measured in a subset of 10 volunteer subjects (prohibitive assay costs prevented measuring drug levels in all subjects). At the beginning of each test day (about 0800 hours), these subjects had a catheter inserted in the cubital vein (inside aspect of the elbow) of the non-dominant arm by a qualified technician. Serial blood samples were taken at the end of each of the eight psychomotor test sessions (one control session and seven post drug ingestion sessions). Each blood sample was 10 ml and the total blood drawn during an experimental session amounted to 80 ml. The blood plasma samples were assayed by a contract laboratory (Algorithme Pharma of Laval, QC, Canada).

Statistical Analysis

The psychomotor test results (dependent variables or number of correct responses for the SUSOPS tasks and 'total score' for the multitask) are plotted over time (independent variable) for each of the five drug conditions, in order to establish the manner in which performance changed over time (8 trials) for each of the drug conditions. Data from the blood assays, and from the sleepiness questionnaire, were also compared across drug conditions. All dependent variables (from all data sets) were submitted to repeated-measures analysis of variance. The Least Significance Difference Test was used for post hoc assessment of any main effects or interactions. The significance level was set at 0.05 for the ANOVAs and for post hoc testing of the significant drug × trial interactions.

RESULTS

The results from all four psychomotor data sets (SRT, LRT, SST, and MT) are illustrated in Fig. 1. The results for each of the four psychomotor data sets were submitted to a two-way repeated-measures ANOVA with five levels of drug (placebo, melatonin, zaleplon, zopiclone, and temazepam) and eight levels of trial (one pre-ingestion trial and seven post ingestion trials). Post hoc testing results of the drug × trial interaction for each of the four tasks are illustrated in Table I.

SRT

The ANOVA (five drugs × eight trials) assessing impact on SRT performance (Fig. 1a) indicates a significant main effect of drugs $F(4,88) = 33.45$ $p < 0.00001$, a significant main effect of trials $F(7,154) = 28.27$ $p < 0.00001$, and a significant drugs × trials interaction $F(28,616) = 10.58$ $p < 0.00001$.

Post hoc testing of the drugs × trials interaction reveals that relative to placebo, there was no impact of melatonin on SRT performance. Zaleplon produced a transient but relatively large drop in performance 1.25 h after ingestion ($p < 0.00001$), which was gone by 2.25 h after dosing. Zopiclone resulted in a large drop in performance ($p < 0.00001$) evident 1.25 h after ingestion and which slowly attenuated over time, not reaching equivalence to placebo until 6.25 h after ingestion. The impact of temazepam on SRT was first evident ($p < 0.009$) 1.25 h after ingestion with the maximum impact not occurring until 2.25 h after ingestion ($p < 0.0001$). This temazepam-induced impact on SRT performance then slowly attenuated over time, reaching placebo equivalence at 4.25 h after ingestion.

LRT

The ANOVA assessing the impact of drugs on LRT performance (Fig. 1b) indicates a significant main effect of drugs $F(4,88) = 14.79$ $p < 0.00001$, a significant main effect of trials $F(7,154) = 19.57$ $p < 0.00001$, and a significant drugs × trials interaction $F(28,616) = 7.64$ $p < 0.00001$.

Post hoc testing of the drugs × trials interaction indicated, again relative to placebo, there was no impact of melatonin on LRT (Table I). The zaleplon impact on LRT was evident 1.25 h after ingestion ($p < 0.00001$), was still present 2.25 h after ingestion ($p < 0.003$), but no longer evident 3.25 h after dosing. Zopiclone resulted in a very large drop in LRT ($p < 0.00001$) evident 1.25 h after ingestion and which slowly attenuated over time, but was still significant at the last psychomotor test session 6.25 h after ingestion ($p < 0.0002$). The impact of temazepam on LRT was not evident until 2.25 h after ingestion ($p < 0.007$), was still present 3.25 h after ingestion ($p < 0.003$), but not 4.25 h after dosing.

SST

The ANOVA assessing the impact of drugs on SST performance (Fig. 1c) yields a main effect of drugs $F(4,88) = 28.88$ ($p < 0.00001$), a significant main effect of trials $F(7,154) = 17.09$ ($p < 0.00001$), and a significant drugs × trials interaction $F(28,616) = 6.42$ ($p < 0.00001$).

Post hoc testing of the drugs × trials interaction indicates that relative to placebo, melatonin did not impact on SST performance. Zaleplon impaired SST performance only at 1.25 h post dosing ($p < 0.00001$). Zopiclone impacted SST performance 1.25 h after ingestion ($p < 0.00001$), with the depth of impact slowly decreasing over time, but still significant at the last psychomotor performance session 6.25 h after dosing ($p < 0.001$). The temazepam-induced effect on SST first occurred at 1.25 h after ingestion ($p < 0.0003$), was still evident at 2.25 h ($p < 0.0003$), and 3.25 h ($p < 0.00002$) after dosing, but was back to placebo levels by 4.25 h after ingestion.

MT

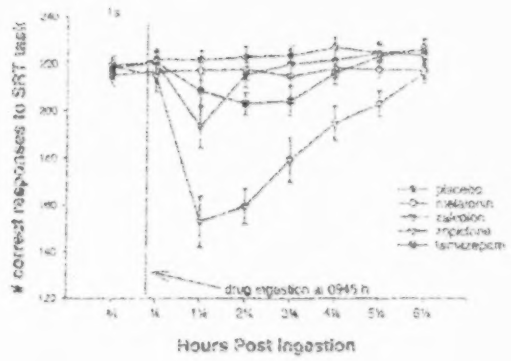
The ANOVA assessing the impact of drugs on MT performance (Fig. 1d) yields a main effect of drugs $F(4,88) = 17.00$ ($p < 0.00001$), a significant main effect of trials $F(7,154) = 10.14$ ($p < 0.00001$), and a significant drugs × trials interaction $F(28,616) = 3.61$ ($p < 0.00001$).

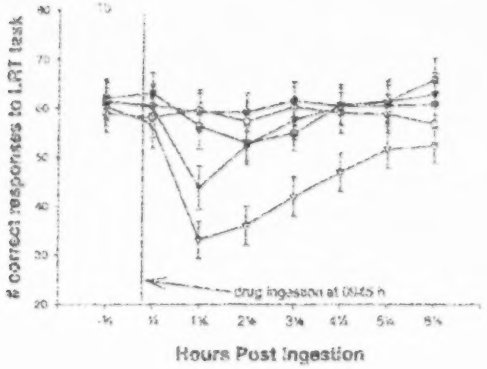
Post hoc testing of the drugs × trials interaction indicates that relative to placebo, melatonin did not impact on MT performance. Further post hoc testing of the drug × trials interaction indicates that zaleplon impacted MT performance within 15 min of ingestion ($p < 0.004$) and again 1.25 h after ingestion ($p < 0.00001$), thereafter remaining at placebo levels. Zopiclone also impacted MT within 15 min of ingestion ($p < 0.0002$), with the peak effect occurring 1 h later at 1.25 h post dosing ($p < 0.00001$), with the depth of impact slowly decreasing until MT performance returned to placebo levels at 4.25 h after ingestion. The impact of temazepam on MT performance was first evident 1.25 h after ingestion ($p < 0.003$), peaked 2.25 h after dosing ($p < 0.00001$), and returned to placebo levels by 3.25 h after ingestion and remained at placebo levels for the balance of the testing period.

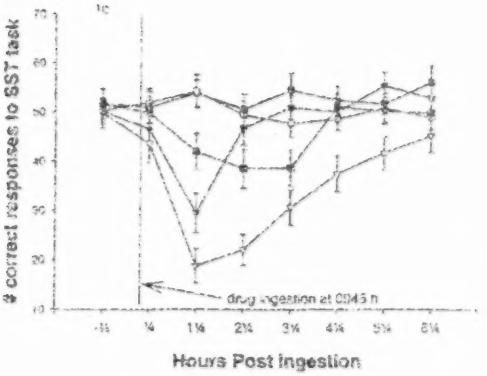
Subjective Sleepiness (Stanford Sleepiness Scale)

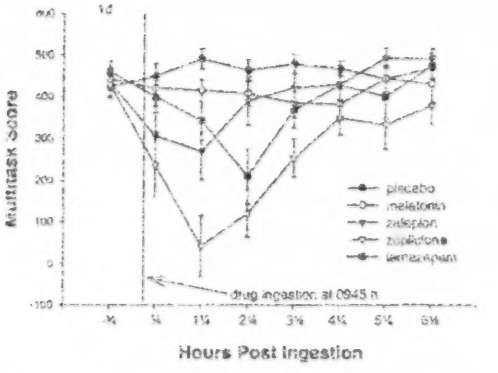
The ANOVA assessing the impact of drugs on subjective sleepiness (Fig. 2) yields a main effect of drugs $F(4,88) = 11.74$ ($p < 0.00001$), a significant main effect of trials $F(7,154) = 15.99$ ($p < 0.00001$), and a significant drugs × trials interaction $F(28,616) = 4.44$ ($p < 0.00001$).

Post hoc testing of the drugs × trials interaction indicates that relative to placebo, melatonin first increased subjective sleepiness 1.25 hours after ingestion ($p < 0.028$). Melatonin-induced sleepiness was briefly not significant 4.25 h after dosing, but reappeared at 5.25 and 6.25 h after ingestion. Zaleplon increased sleepiness scores within 15 min of ingestion ($p < 0.004$), peaking at 3.25 h post ingestion ($p < 0.0001$). On zaleplon, peak sleepiness occurred 1.25 h after ingestion ($p < 0.00001$), and remained significant until 3.25 h after dosing. Peak sleepiness on zopiclone occurred 1.25 h after ingestion ($p < 0.00001$) and remained significantly elevated beyond the monitored period.









While temazepam caused a significant increase in sleepiness at 1.25 h ($p < 0.0001$), peak sleepiness did not occur until 2.25 h after ingestion. Temazepam-induced sleepiness was still evident 4.25 h after dosing but not thereafter.

Blood Plasma

The plasma levels of each medication are plotted over trials in Fig. 3 and were analyzed in four separate one-way repeated-measures ANOVA over the eight trials.

Post hoc testing reveals that plasma melatonin levels (Fig. 3a) were significantly elevated by 1.75 h post ingestion ($p < 0.00001$), and remained elevated until 3.75 h post ingestion ($p < 0.0001$). Zaleplon levels increased significantly by 0.75 h after ingestion ($p < 0.00001$), peaking 1.75 h after ingestion, and returning to pre-ingestion levels by 4.75 h after dosing. In contrast, while plasma zopiclone levels also peaked 1.75 h post ingestion ($p < 0.00001$), they were still very high at the end of the day ($p < 0.00001$) 6.75 h after dosing. Temazepam plasma levels were slower to peak at 2.75 hours post ingestion ($p < 0.000001$) and were also still very high at the end of day ($p < 0.000002$).

DISCUSSION

All drug conditions in this study induced effects on either subjective levels of sleepiness or on task performance. Melatonin caused no effect on performance, with increasing effects noted with zaleplon, temazepam, and zopiclone, respectively.

Melatonin is a naturally occurring hormone synthesized by the pineal gland from the precursor amino acid tryptophan. In pharmacologic doses, melatonin has a large margin of safety, producing a mild soporific effect with minimal side-effects (6). This along with melatonin's ability to advance or retard circadian rhythms depending on dosage and the timing of ingestion, has resulted in increased research interest (1,21,24). One study showed that aircrew who were administered melatonin on a long transmeridian mission had improved sleep patterns and fewer errors on a choice reaction time task after arrival (8). Some studies have documented small decrements in simple auditory reaction time and visual serial choice reaction time (9,37), whereas another study (1) found no difference in a logical reasoning task or in a letter cancellation task. The effects of melatonin on human performance are controversial.

In this study, melatonin produced significant increases in subjective sleepiness within 1.25 h of ingestion (Fig. 2, **Table II**), but it did not impact performance even though plasma levels of melatonin were significantly elevated between 1.75 h and 4.75 h post dosing. This is a somewhat curious result. The large majority of research assessing the effects of melatonin on psy-

Fig. 1. Number of correct responses to the Serial Reaction Time (SRT), Logical Reasoning (LRT), and Serial Subtraction task (SST), as well as 'multitask score' in Figs. 1a, 1b, 1c, and 1d respectively. All values are (mean ± SEM) and are plotted over 'drugs' and 'hours post ingestion'.

TABLE I. POST HOC RESULTS FOR ALL FOUR PSYCHOMOTOR TASKS, WHERE EACH OF THE FOUR EXPERIMENTAL DRUGS IS COMPARED TO PLACEBO OVER EIGHT TRIALS.

Task	Drug	Time in Hours, Relative to Drug Ingestion							
		-½	½	1½	2½	3½	4½	5½	6½
SRT	Melatonin	ns	ns	ns	ns	ns	ns	ns	ns
	Zaleplon	ns	ns	0.00001	0.003	ns	ns	ns	ns
	Zopiclone	ns	ns	0.00001	0.00001	0.00001	0.00001	0.0001	ns
	Temazepam	ns	ns	0.009	0.0001	0.0001	ns	ns	ns
LRT	Melatonin	ns	ns	ns	ns	ns	ns	ns	ns
	Zaleplon	ns	ns	0.00001	0.003	ns	ns	ns	ns
	Zopiclone	ns	ns	0.00001	0.00001	0.00001	0.00001	0.0001	0.0002
	Temazepam	ns	ns	ns	0.007	0.003	ns	ns	ns
SST	Melatonin	ns	ns	ns	ns	ns	ns	ns	ns
	Zaleplon	ns	ns	0.00001	ns	ns	ns	ns	ns
	Zopiclone	ns	ns	0.00001	0.00001	0.00001	0.0001	0.002	0.001
	Temazepam	ns	ns	0.0003	0.0003	0.00002	ns	ns	ns
MT	Melatonin	ns	ns	ns	ns	ns	ns	ns	ns
	Zaleplon	ns	0.004	0.00001	ns	ns	ns	ns	ns
	Zopiclone	ns	0.0002	0.00001	0.00001	0.0001	ns	ns	ns
	Temazepam	ns	ns	0.003	0.00001	ns	ns	ns	ns

ns = not significant at 0.05, or respective p values.

chomotor performance is based on regular-release melatonin. The melatonin used in this study was a time-released formulation (Circadin®) that contains a pharmaceutical vehicle which delays delivery of melatonin, somewhat mimicking a more physiologic release relative to the pharmacologic delivery afforded by regular-release melatonin. One possible reason we found no impact of melatonin may be due to the fact that because we used time-released melatonin, the blood levels of melatonin were lower than had we used regular release melatonin. Regular release melatonin would likely have produced higher blood levels, in the nanogram per milliliter range, as compared with the picogram/milliliter melatonin blood levels found in our subjects.

Circadin® is a regulatory grade sustained-release formulation of melatonin. In many countries, melatonin is sold as an over-the-counter supplement unregulated as to purity and concentration. This makes it unattractive for operational use. However, in jurisdictions where melatonin is regulated as to purity and dosage, it could be used in support of military operations as a mild, normally well-tolerated soporific which has been demonstrated to facilitate early circadian sleep in our laboratory (24).

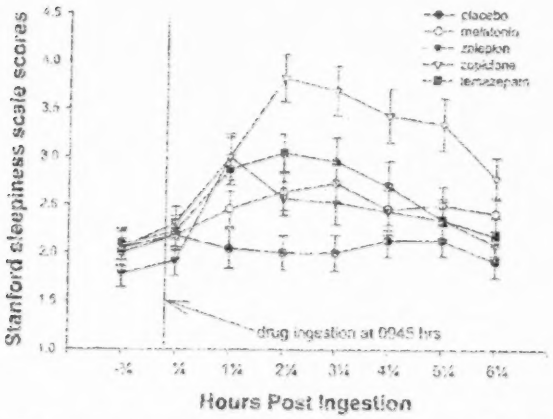
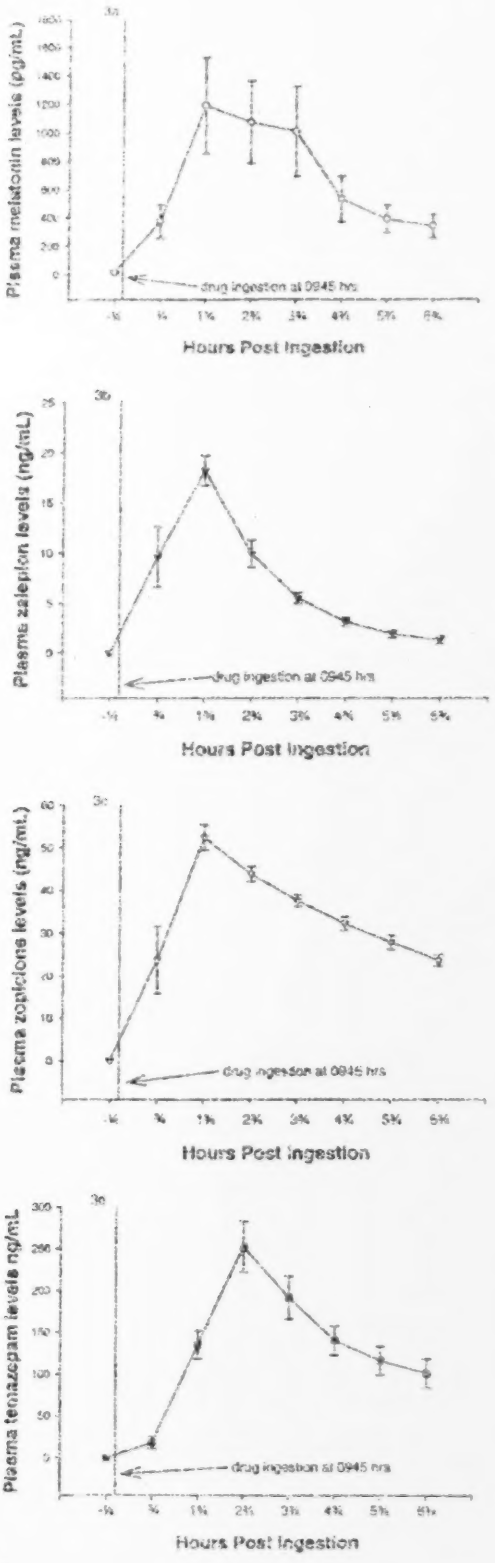


Fig. 2. Subjective sleepiness scores (Stanford Sleepiness Scale). All values are (mean ± SEM) and are plotted over 'drugs' and 'hours post ingestion'.

Zaleplon, a new pyrazolopyrimidine hypnotic marketed as Starnoc® in Canada, has a short half-life of about 1 h, which could make it useful in support of military operations (13). While zaleplon can be used to treat initial insomnia at the beginning of the night, its short half-life has proven it effective in the treatment of middle insomnia (difficulty returning to sleep after awakening), allowing patients to take it later in the night and still be free of residual effects in the morning. Vermeeren et al. have demonstrated that "Zaleplon 10 mg certainly, and 20 mg probably, can be taken at bedtime or later in the night, up to 5 h before driving with little risk of serious impairment" (32).

In our study, zaleplon produced a significant but short-lived impact (varying from 1.25 to 2.25 h) on all four psychomotor tasks (Fig. 1), and a 2-h period of increased sleepiness (Fig. 2, Table II). The plasma levels of zaleplon were back to placebo level 4.75 h post ingestion (Fig. 3b). Zaleplon, in the dose we used, lived up to its reputation as a short acting medication that causes transient performance impairment, has significant short-acting hypnotic power and is quickly eliminated. Zaleplon would be a good choice of medication to facilitate sleep where there may be a limited window for sleep of only a few hours. Zaleplon might also be safely used for middle insomnia with a similar limited sleep window of several hours before duty.

Zopiclone, marketed as Imovane® in Canada, is a cyclopyrrolone derivative with a half-life of approximately 4 h (10,20) and is reputed to produce a short-acting sedative/hypnotic effect. Zopiclone has been reported to be beneficial to sleep architecture by causing an increase in SWS (slow wave sleep) (14). After a normal sleep period on 7.5 mg, the standard clinical dose, several studies have failed to find any impact of


Plasma melatonin levels (pg/mL)
drug ingestion at 0945 hrs
Hours Post Ingestion
Plasma zaleplon levels (ng/mL)
drug ingestion at 0945 hrs
Hours Post Ingestion
Plasma zopiclone levels (ng/mL)
drug ingestion at 0945 hrs
Hours Post Ingestion
Plasma temazepam levels ng/mL
drug ingestion at 0945 hrs
Hours Post Ingestion

zopiclone on psychomotor performance (4,5,30). Various studies also investigated the residual effects of zopiclone almost immediately after ingestion (29,30,33). For instance, Subjan and Hindmarch (30) found increased reaction times for a memory scan task 1 h after drug ingestion, but no impact on performance 10 h after ingestion. Warot et al. (33) used flicker fusion, choice reaction time, digit symbol substitution, and memory tests and found no impairment beyond 6 h after ingestion.

In this study, zopiclone produced the largest impact on sleepiness and on performance of all four medications. The impact on sleepiness was evident from 1.25 h after ingestion through to the end of the experimental day (Fig. 2, Table II). Similarly, the impact on performance was also evident from 1.25 h after dosing, where the impact was greatest, after which the effect slowly dissipated, reaching placebo levels for the SRT task only for the last test session at 6.25 h after ingestion (Fig. 1). For the LRT and SST tasks, the zopiclone-induced impact on performance was still significant at the last psychomotor test session of the day, 6.25 h after dosing. Multitask performance recovered to placebo levels at 4.25 h after ingestion. Zopiclone plasma levels were still very high at the end of the experimental day (Fig. 3c). These results suggest that for a 7.5-mg dose of zopiclone, a minimum post ingestion time to duty of 8 h would be advisable.

Temazepam is one of the minor metabolites of diazepam (3-hydroxydiazepam) and is used in the short-term relief of initial insomnia (difficulty in falling asleep), middle insomnia (difficulty returning to sleep after nocturnal awakening), and/or early morning awakenings (19). Although benzodiazepines improve sleep continuity, they reduce slow wave sleep (SWS) and rapid eye movement (REM) sleep (23).

The typical European doses for temazepam are 20 mg or 30 mg, while the North American doses are 15 mg or 30 mg. A soft gelatin capsule was developed in the United Kingdom because of problems with the absorption of temazepam in the hard-shell gelatin capsule or tablet format. The North American temazepam formulations of hard-shell gelatin capsules are more slowly absorbed than the European formulation and are less effective at improving sleep latency (27). The 20-mg temazepam doses in soft gelatin capsules has an elimination half-life of 5 to 7 h; while the hard gelatin capsules have a plasma elimination half-life ranging from 8 to 22 h (12).

Research over the past two decades has established that acute administration of benzodiazepines has adverse effects on memory, attention, and psychomotor speed (18,36). Porcu et al. (26) used a 20-mg dose of temazepam to improve the quality and quantity of daytime sleep, resulting in improved wakefulness during the night. Recently, Caldwell et al. (7) used 16 U.S. Army helicopter pilots to demonstrate the efficacy of a 30 mg dose of temazepam in prolonging daytime sleep

Fig. 3. Drug plasma levels for each of melatonin (picograms/ml), zaleplon (nanograms/ml), zopiclone (nanograms/ml), and temazepam (nanograms/ml). All values are (mean ± SEM) and are plotted over "hours post ingestion."

TABLE II. POST HOC RESULTS FOR SUBJECTIVE SLEEPINESS (STANFORD SLEEPINESS SCALE), WHERE EACH OF THE FOUR EXPERIMENTAL DRUGS IS COMPARED TO PLACEBO OVER EIGHT TRIALS.

		Time in Hours, Relative to Drug Ingestion							
Parameter	Drug	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	$2\frac{1}{4}$	$3\frac{1}{4}$	$4\frac{1}{4}$	$5\frac{1}{4}$	$6\frac{1}{4}$
Subjective Sleepiness	Melatonin	ns	ns	0.028	0.0007	0.0001	ns	0.048	0.005
	Zaleplon	ns	ns	0.00001	0.003	0.005	ns	ns	ns
	Zopiclone	ns	ns	0.00001	0.00001	0.00001	0.00001	0.00001	0.00004
	Temazepam	ns	ns	0.0001	0.00001	0.00001	0.006	ns	ns

ns = not significant at 0.05, or respective p values.

to attenuate the effects of shift lag and to attenuate the normal nighttime drop in performance. Caldwell et al. concluded that physicians should be careful to ensure the aviator has a minimum of 8 h in which to sleep after taking temazepam.

The 15-mg dose of temazepam used in this study caused an impact on performance on all four tasks, lasting for 2 to 3 h depending on the task (Fig. 1). Temazepam-induced sleepiness was evident between 1.25 and 4.25 hours post dosing (Fig. 2, Table II). Temazepam plasma levels were still elevated after the last blood sample was taken at 6.75 h after ingestion (Fig. 4d), reflecting its known longer half-life. That temazepam had less impact on performance than zopiclone was surprising. However, Hindmarch (16) did suggest that "it seems that temazepam 15 mg is too low a dose to be very effective as an hypnotic." Tiplady et al. (31) have determined that the dose-response curve of temazepam is a positively accelerating one, with performance effects being proportional to the square of the dose. Begg et al. (3) concluded that if this quadratic relationship holds, 30 mg would produce about double the impairment of 20 mg and in fact demonstrated this relationship. Quite possibly, had we used a 30-mg dose of temazepam, we would have measured more temazepam-induced performance impairment. The long half-life and relatively lower efficacy of temazepam in inducing sleepiness suggest that for a longer-acting hypnotic, zopiclone with its reported benefit on slow-wave sleep (14) might be preferable for sleep hygiene in situations where a minimum sleep period of 7–8 h is guaranteed before return to duty.

CONCLUSIONS

This study compared the effects of melatonin, zaleplon, zopiclone, and temazepam on psychomotor performance and subjective sleepiness for a 6.75-h period after acute ingestion. Melatonin caused no effect on performance, with increasing effects noted with zaleplon, temazepam, and zopiclone, respectively. Melatonin (as the 6 mg time release formulation Circadin®) produced no impact on psychomotor performance in spite of having produced a prolonged period of subjective sleepiness. Zaleplon (Starnoc®) produced a short-acting effect on sleepiness and performance. The 7.5-mg dose of zopiclone (Imovane®) produced a sustained effect on sleepiness and impacted performance beyond the 6.75 h period of observation in this study. Temazepam (Restoril®), in the 15-mg hard-gelatin formulation used in this study, while resulting in sustained elevated drug levels beyond 6.75 h, produced less sustained subjective sleepiness with less effect on performance than the 7.5-mg dose of zopiclone.

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